Review

Clinical review: Positive end-expiratory pressure and cardiac output

Thomas Luecke[1] and Paolo Pelosi[2]

[1]Section Head, Critical Care, Department of Anesthesiology and Critical Care Medicine, University Hospital of Mannheim, Germany
[2]Associate Professor in Anaesthesia and Intensive Care, Dipartimento di Scienze Cliniche e Biologiche, Università degli Studi dell'Insubria, Varese, Italy

Corresponding author: Thomas Luecke, thomas.luecke@anaes.ma.uni-heidelberg.de

Published online: 18 October 2005
This article is online at http://ccforum.com/content/9/6/607
© 2005 BioMed Central Ltd

Critical Care 2005, **9**:607-621 (DOI 10.1186/cc3877)

Abstract

In patients with acute lung injury, high levels of positive end-expiratory pressure (PEEP) may be necessary to maintain or restore oxygenation, despite the fact that 'aggressive' mechanical ventilation can markedly affect cardiac function in a complex and often unpredictable fashion. As heart rate usually does not change with PEEP, the entire fall in cardiac output is a consequence of a reduction in left ventricular stroke volume (SV). PEEP-induced changes in cardiac output are analyzed, therefore, in terms of changes in SV and its determinants (preload, afterload, contractility and ventricular compliance). Mechanical ventilation with PEEP, like any other active or passive ventilatory maneuver, primarily affects cardiac function by changing lung volume and intrathoracic pressure. In order to describe the direct cardiocirculatory consequences of respiratory failure necessitating mechanical ventilation and PEEP, this review will focus on the effects of changes in lung volume, factors controlling venous return, the diastolic interactions between the ventricles and the effects of intrathoracic pressure on cardiac function, specifically left ventricular function. Finally, the hemodynamic consequences of PEEP in patients with heart failure, chronic obstructive pulmonary disease and acute respiratory distress syndrome are discussed.

Introduction

Cyclic opening and closing of atelectatic alveoli and distal small airways with tidal breathing is known to be a basic mechanism leading to ventilator-induced lung injury [1]. To prevent alveolar cycling and derecruitment in acute lung injury, high levels of positive end-expiratory pressure (PEEP) have been found necessary to counterbalance the increased lung mass resulting from edema, inflammation and infiltrations and to maintain normal functional residual capacity (FRC) [2]. Therefore, application of high levels of PEEP is often recommended [3], despite the fact that 'aggressive' mechanical ventilation using high levels of PEEP to maintain or restore oxygenation during acute lung injury can markedly affect cardiac function in a complex and often unpredictable fashion. Likewise, this notion holds true for intrinsic PEEP caused by ventilation with high respiratory rates resulting in dynamic hyperinflation. Except from the failing ventricle, PEEP usually decreases cardiac output, a well known fact since the classic studies of Cournand *et al.* [4], in which the effects of positive-pressure ventilation were measured. They concluded that positive-pressure ventilation restricted the filling of the right ventricle because the elevated intrathoracic pressure (ITP) restricted venous flow into the thorax and, thereby, reduced cardiac output. This formulation of intrathoracic responses to positive-pressure ventilation still is the basis of our present day understanding of the cardiopulmonary interactions induced by PEEP, although precise responses to PEEP have not been simple to prove, and the intrathoracic responses appear multiple and complex.

As heart rate usually does not change with PEEP [5], the entire fall in cardiac output is a consequence of a reduction in left ventricular (LV) stroke volume (SV). Therefore, the discussion on PEEP-induced changes in cardiac output can be confined to analyzing changes in SV and its determinants: preload, afterload, contractility and ventricular compliance.

Before considering how PEEP affects the determinants of SV, it has to be emphasized that ventilation with PEEP, like any other active or passive ventilatory maneuver, primarily affects cardiac function by changing lung volume and ITP [6]. To understand the direct cardiocirculatory consequences of respiratory failure, one must, therefore, understand the effects of changes in lung volume, factors controlling venous return, the diastolic interactions between the ventricles and the effects of ITP on cardiac function, specifically LV function.

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ARDSexp = extrapulmonary ARDS; ARDSp = pulmonary ARDS; C_{CW} = chest wall compliance; CHF = congestive heart failure; C_L = lung compliance; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; ESPVR = end-systolic pressure-volume relationship; FRC = functional residual capacity; IAP = intra-abdominal pressure; ITP = intrathoracic pressure; LV = left ventricular; PaCO2 = arterial carbon dioxide partial pressure; Palv = avleolar pressure; Paw = airway pressure; P_{CRIT} = critical closing pressure; PEEP = positive end-expiratory pressure; Pes = esophageal pressure; Pms = mean systemic pressure; Ppc = pericardial pressure; Ppl = pleural pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricular; SV = stroke volume.

This review will attempt to integrate basic mechanisms into the global mechanisms of PEEP, and relate these concepts to patient care. Analysis will focus on the relationships between lung volume and ITP and using these relationships to assess specifically the four primary components of the circulatory system that are affected by ventilation (systemic venous return, right ventricular (RV) output, LV filling, and LV output) [7]. Subsequent analysis will be confined to controlled mechanical ventilation and it needs to be emphasized that hemodynamic effects during assisted spontaneous ventilation, compared to controlled ventilation, may be substantially different due to the difference in ITP.

Relationship between airway pressure, intrathoracic pressure and lung volume

A lot of confusion exists, both in the literature and at the bedside, in understanding and applying the concept of ITP during mechanical ventilation. As outlined by Scharf [8], it must be clear that the term 'intrathoracic pressure' does not *per se* specify a pressure. Rather, one must ask, "which intrathoracic pressure, esophageal, pleural, cardiac fossa, or cardiac surface?" To make things even worse, it is common practice to equate changes in airway pressure (Paw) with changes in both ITP and lung volume.

Although positive-pressure ventilation increases lung volume only by increasing Paw, the degree to which both ITP (being esophageal, pleural or pericardial) and lung volume increase will be a function of airway resistance as well as lung and chest wall compliance.

Lateral chest wall pleural pressure (Ppl) and pericardial pressure (Ppc) increase similarly in normal and acute lung injury states for a constant tidal volume despite widely varying lung compliance and a greater mean and plateau Paw during the acute lung injury condition [9,10]. The primary determinant of the increase in Ppl and Ppc during positive-pressure ventilation is lung volume change [11]. During sustained increases in lung volume, the increase in Ppl is greater than the increase in Ppc. Thus, estimating Ppc by measuring Ppl on any surface within the thorax may still underestimate actual Ppc, which is LV surrounding pressure [10]. Changes in Ppl induced by positive-pressure ventilation are not the same in all regions of the thorax; Ppl at the diaphragm increases least, and juxtacardiac Ppl increases most [12]. These differences are in addition to the normally described hydrostatic pressure gradient in the pleural space from the posterior to anterior surface. As lung injury is often non-homogeneous, large increases in Paw are often seen during mechanical ventilation in such patients even when the absolute tidal volume is low. This increased Paw should over-distend these aerated lung units [13]. However, two separate studies have demonstrated that, despite this non-homogeneous alveolar distention, if tidal volume is kept constant, the Ppl will increase equally, independent of the mechanical properties of the lung [9,14]. Thus, if tidal volume is kept constant, changes in peak and mean Paw will reflect changes in the mechanical properties of the lungs and patient cooperation, but will not reflect changes in Ppl nor alter global dynamics of the cardiovascular system [10]. As demonstrated by Pinsky and coworkers [15] in postoperative patients, however, the percentage of Paw that will be transmitted to the pericardial surface is not constant from one subject to the next as PEEP is increased. Furthermore, the degree to which Ppc will increase relative to Ppl is a function of prior pericardial constraint [10].

Bearing in mind that the heart is a pressure chamber within a pressure chamber (i.e. the thorax), the question of how much of externally applied Paw (or PEEP) is actually transmitted to the intrathoracic structures is of pivotal importance, especially if one tries to measure and interpret filling pressures of the heart in order to define its loading conditions. In addition, as the heart is a pressure chamber within the pericardium, it is also pericardial pressure applied over the surface of the atria and ventricles that affect transmission of pressure to the intracardial chambers, varying both with respiratory and cardiac cycles and producing different surface pressures over the four cardiac chambers during these cycles. The catheter (central venous or pulmonary artery) measures an intravascular pressure, relative to atmosphere. The interpretation of hemodynamic data during positive-pressure ventilation, however, requires thinking in terms of transmural pressures, which is the pressure difference acting across the wall of a vessel or cardiac chamber (i.e. inside minus outside pressure). As neither the Ppc, which is the outside pressure for the right and left ventricle, nor the Ppl are directly accessible in clinical practice, the esophageal pressure (Pes) is commonly used as the outside pressure. Thus, transmural LV pressure would clinically be measured as LV intracavitary pressure minus Pes, assuming that Pes represents cardiac surface pressure.

While this is a common assumption, there are potential pitfalls with that approach: Ppc may not increase as much as juxtacardiac Ppl during positive-pressure ventilation, especially in heart failure states. Presumably, as total cardiac volume decreases with the application of positive Paw, its venous return decreases and/or left ventricular ejection increases [10]. Under these common conditions, if pericardial restraint was limiting cardiac filling (i.e. Ppc exceeds juxtacardiac Ppl), the pericardium will become less of a limiting membrane [16]. Ppc is the surrounding pressure for ventricular distention. Thus, estimates of Ppc made by using Ppl (Pes) measurements may overestimate surrounding pressure as Ppl is increasing.

In summary, one is faced with two important limitations rendering the assessment of PEEP-induced changes in cardiac function difficult. First, true transmural ventricular filling pressures are not available and surrogate estimates using Pes have to be used instead. Second, predicting how

much Paw is transmitted to the pericardial space is difficult at best. According to O'Quin and Marini [17], one can estimate how changes in avleolar pressure (ΔPalv) translate into changes in ITP (ΔITP), assuming that the compliances of the lung (C_L) and chest wall (C_{CW}) are in series and homogeneous:

$$\Delta ITP/\Delta Palv = 1/(1+ C_{CW}/C_L)$$

C_{CW}/C_L is not generally known with precision, and the validity of the underlying assumptions is rather approximate. Nevertheless, the above relationship is helpful for making rough predictions. In most healthy subjects, C_L is nearly the same as C_{CW} during normal tidal volume (0.2 L/cmH_2O). In this situation, ΔITP/ΔPalv = ½ or half of the applied PEEP would be expected to be transmitted to ITP. Whereas a popular rule of thumb is to subtract half of the applied PEEP from hemodynamic measurements, this rule is helpful only when the patient's chest wall and lung compliance are normal [18]. A decrease in lung compliance has been shown to decrease the transmission of Paw to intrathoracic structures (commonly measured as Ppl) [19,20], while these findings have been challenged by O'Quin and Marini [17], who measured juxtacardiac Ppl and found that the fractional change of Ppl versus Paw was only slightly decreased after acute lung injury in a canine model. These results were confirmed by Scharf and Ingram [14] and Romand *et al.* [9], who showed that the primary determinant of change in Ppl (or ITP) during positive-pressure breathing is the amount of lung inflation, not a specific change in compliance. Thus, the PEEP-induced change in total intrathoracic volume, which actually has to be considered in the diseased lung, when total volume can be increased due to extensive edema even if aerated lung volume is actually decreased, ultimately determines the changes in ITP and the concomitant hemodynamic effects.

In summary, it is extremely difficult to predict the amount to which increases in Paw, either induced by PEEP or positive-pressure ventilation, will increase ITP in an individual patient with acute lung injury. Pes may serve as a reasonable estimate for Ppl and Ppc, but is one step removed from these values and may underestimate increases in either Ppl or Ppc when lung volumes also increase [10]. Nevertheless, when trying to understand the hemodynamic effects of PEEP in an individual patient, the most important question to keep in mind is: to what extend will PEEP change total lung volume and ITP and how will these changes ultimately affect LV preload, contractility and afterload?

Effects of PEEP

As proposed by Pinsky [6], all hemodynamic effects of positive-pressure ventilation and PEEP can simply be grouped into processes that, by changing lung volume and ITP, affect left ventricular preload, afterload and contractility (Fig. 1).

Left ventricular preload

The effects of PEEP on LV preload are dependent on changes in systemic venous return, RV output and LV filling. Due to the complexity of these changes, the single factors will be discussed separately.

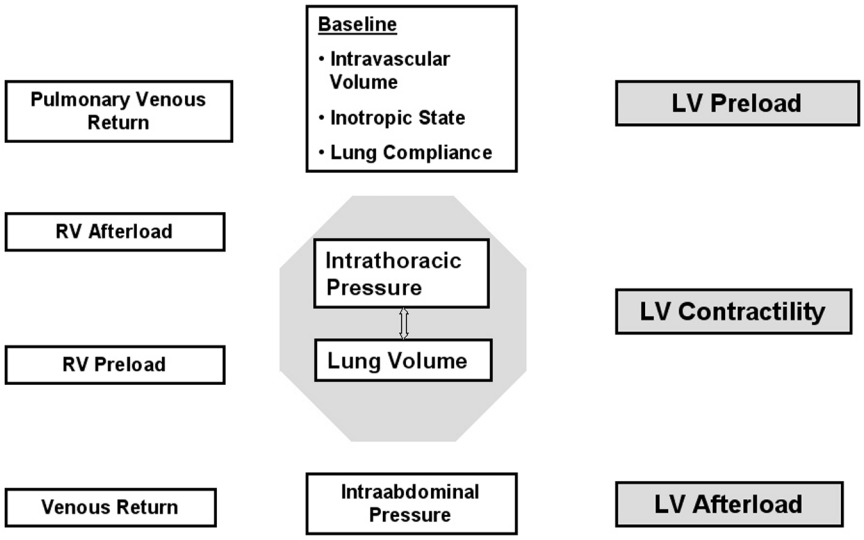
PEEP and the determinants of systemic venous return

Determinants of venous return

In steady state, cardiac output must equal the return of blood to the heart. This in turn is determined by the mechanical characteristics of the circuit, which is called circuit function. This includes stressed vascular volume, venous compliance, resistance to venous return and the outflow pressure for the circuit, which is right atrial pressure (RAP). RAP is controlled by cardiac function and the interaction of cardiac function and circuit function determine cardiac output [21]. An important concept for the understanding of venous return is that of stressed and unstressed volume. The venous system, like any other elastic structure, will fill with a certain volume, called the 'unstressed' volume, without changing the pressure or causing distention of the structures. Unstressed volume represents as much as 25% of total blood volume and constitutes a significant reservoir for internally recruiting volume into the system. The difference between the total volume in the system and the unstressed volume is the relevant volume for causing pressure in the filling chamber, the stressed volume [8]. The equivalent pressure in the veins and venules to the hydrostatic pressure filling the system is called mean systemic pressure (Pms). It is determined by the volume filling the veins and the compliance of the veins. The term that is used for describing the relationship of the total volume for a given pressure is 'capacitance' and takes into account both stressed and unstressed volume. This is not to be confused with the term compliance, which is the change in volume for the change in pressure [21]. In summary, the determinants of venous return are the stressed volume (i.e. the difference between total volume and unstressed volume), venous compliance, resistance to venous return, and RAP. Venous return is maximal when RAP equals zero. An increase in venous return comes from an increase in stressed volume, decrease in venous compliance, decrease in resistance to venous return and a decrease in RAP. Vascular capacitance is determined by the tone in the walls of the small venules and veins. Contraction of smooth muscles in these vessels due to neurosympathetic activation or exogenous catecholamines can decrease venous capacitance by converting unstressed volume into stressed volume, thus raising mean systemic pressure [21].

The sensitivity of systemic venous return to respiratory-induced changes has been described in the classic experiments by Guyton and colleagues [22,23]. The basic principle is that systemic venous return is the major determinant of circulation and is equal to left ventricular output under steady state conditions [7,24,25]. Guyton *et al.* [23] demonstrated that RAP represents the outflow pressure

Figure 1



Schematic representation of potential cardiopulmonary interactions with changes in intrathoracic pressure (ITP) and lung volume (redrawn with permission from [137]). To obtain a more focused view of these numerous interactions, one can simply group all hemodynamic effects of ventilation into processes that, by changing lung volume and ITP, affect left ventricular (LV) preload, contractility and afterload [6]. RV, right ventricular.

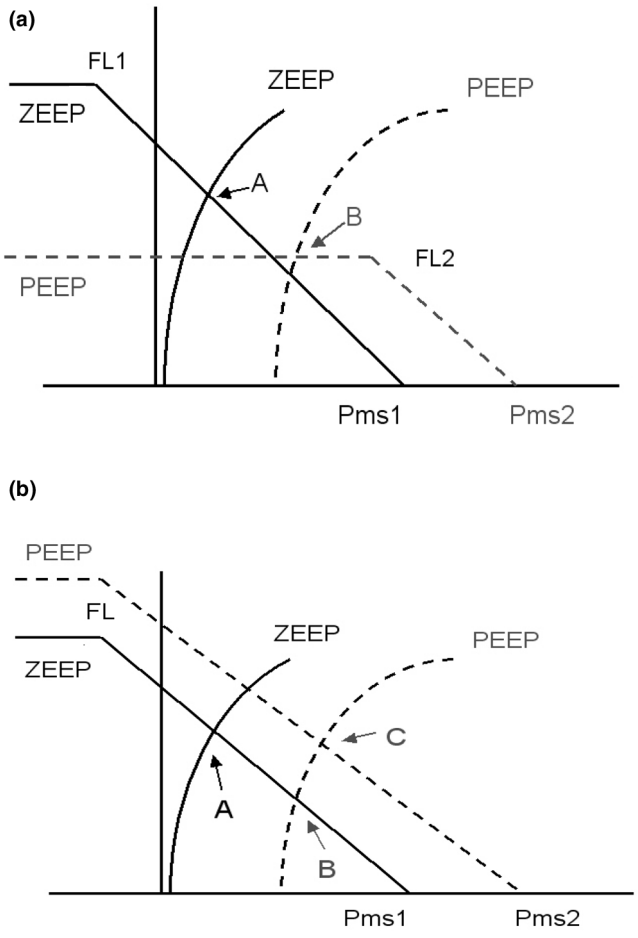
(backpressure) for venous return. The relationship between RAP and venous return is displayed by the venous return curve. The pressure gradient driving blood from the periphery to the right atrium can be defined as the difference between the pressures in the upstream reservoirs, the Pms relative to RAP. Pms, defined as the RAP at the point of zero flow, is a function of blood volume, peripheral vasomotor tone and the distribution of blood within the vasculature [26]. As RAP increases, venous return decreases until RAP equals Pms. As RAP decreases, venous return increases until the point of flow limitation. The slope of the venous return curve is equal to 1/resitance to venous return. The relationship between right atrial end-diastolic pressure (representing preload) and cardiac output is the familiar Frank-Starling relationship [8]. The superimposition of the venous return curve and the Frank-Starling curve on the same set of axes was the creative insight of Guyton [22] and provided an immensely useful conceptual framework for studying cardiovascular control [27]. Because, in steady state, cardiac output must equal venous return, the point at which the two systems exist in equilibrium is represented by the point of intersection of the cardiac function (Frank-Starling) and venous return curves [8]. Thus, for any given set of cardiac function and venous return curves there exists only one combination of RAP and cardiac output (= venous return) at which steady-state conditions apply (Fig. 2, point A).

Effect of PEEP on venous return

As the right atrium is a highly compliant structure, RAP would reflect variations in ITP. Any increase in PEEP, by increasing lung volume, and thus ITP, is expected to decrease venous return by decreasing the pressure gradient in a manner demonstrated in Fig. 2. The cardiac function curve is displaced rightward by the amount by which ITP is increased, thus maintaining the same transmural pressure-cardiac output relationships. Postulating that Pms does not change with PEEP, this would move the intersection of the cardiac function and the venous return curves 'downward' on the venous return curve (Fig. 2a, point B) [8]. As a result, the gradient for venous return decreases, decelerating venous blood flow [28], decreasing RV filling and, consequently, decreasing RV SV [28-32].

However, as suggested by Scharf *et al*. [33] and later demonstrated in experimental studies [34,35], PEEP also increases Pms, thus preserving the gradient for venous return. Jellinek and coworkers [36] confirmed that positive Paw equally increased RAP and Pms in patients during general anesthesia for implantation of defibrillator devices. This increase in Pms, which may be due to an increase in stressed volume or sympathoadrenal stimulation, could buffer the PEEP-induced decrease in venous return and shift the equilibrium point towards higher values of cardiac output (Fig. 2a, point C). In addition to the effects of increased ITP, it should be emphasized, however, that the actual compliance of the right atrium is substantially defined by the pericardium. As demonstrated by Tyberg and coworkers [37], as volume is increased, the compliance of the entire right atrium is constrained by the pericardium, thus markedly decreasing the effective compliance of the right atrium. Tyberg and colleagues' work suggests that RAPs relative to atmosphere as low as 5 mmHg are beginning to reflect pericardial

Figure 2



Effects of positive end-expiratory pressure (PEEP) on venous return and cardiac output. **(a)** Theoretical effects of PEEP on venous return (VR) and cardiac output (CO). PEEP causes an increase in intrathoracic pressure (ITP) and a right shift in the cardiac function curve. If there were no change in the VR curve, then CO and VR would decrease (from point A to point B). However, if there is a compensatory increase in mean systemic pressure (from Pms1 to Pms2), then the system will exist in equilibrium at point C, at which VR and CO would be maintained compared to zero end-expiratory pressure (ZEEP) conditions. Pms can increase either by an increase in stressed volume or sympathoadrenal stimulation. **(b)** Another possible scheme for the changes in VR with PEEP. If there is an increase in the pressure at which flow limitation occurs, then the ability of an increase in Pms to buffer PEEP-induced decreases in VR is markedly less. FL1, flow limiting point at ZEEP; FL2, flow limiting point at PEEP. Modified from [8], with permission.

constraint and that pressures exceeding 10 to 12 mmHg are dominated by pericardial constraint.

Tyberg *et al.* [38] also measured RV filling pressure defined as RAP minus Ppc in patients undergoing elective cardiac surgery. They demonstrated that RV filling pressure was insignificantly altered by acute volume loading. While RAP increased with volume loading, however, Ppc also increased so that RV filling pressures remained unchanged. Thus, under normal conditions, RV diastolic compliance is greater than pericardial compliance. With RV filling, right heart sarcomere length probably remains constant, and conformational changes in the RV more than wall stretch are responsible for RV enlargement [16]. Another study in postoperative surgical patients [39] showed that when the RV end diastolic volume was reduced by application of PEEP, both RAP and Ppc increased, but RV filling pressure remained constant. Thus changes in RAP do not follow changes in RV end diastolic volume. The exact quantification of these mechanical heart-pericardium-lung interactions is difficult in clinical practice, however.

Whereas the pressure gradient for venous return (Pms-RAP) was not altered by PEEP in the studies cited above [34-36], venous return and cardiac output invariably fell, indicating an increase in resistance of the venous conduits. According to Fessler *et al.* [34], PEEP may either: decrease the caliber of the conducting veins by constriction or compression, resulting in reduced flow at the same driving pressure through an increase in ohmic resistance (e.g. by abdominal pressurisation); or increase the pressure around a portion of the veins in excess of RAP.

If RAP were below a critical closing pressure (P_{CRIT}) of the veins, a condition termed a 'vascular waterfall' is said to exist. This term was first applied to blood flow through the pulmonary circulation when alveolar pressure exceeded left atrial pressure [40]. Under these circumstances, the effective downstream pressure for venous return is P_{CRIT}, not RAP. If PEEP were to elevate P_{CRIT} in some parts of the circulation in excess of RAP, then the effective pressure gradient for venous flow from those regions could fall despite an unaltered (Pms-RAP) difference [41], flow limitation at PEEP would occur at higher pressures compared to ZEEP and the ability of an increased Pms to buffer the PEEP-induced decrease in venous return would be markedly less (Fig. 2b, point B). In fact, Fessler and coworkers [42] demonstrated a PEEP-induced vascular collapse at the inferior vena cava in canine studies, consistent with a vascular waterfall [43] or zone 2 condition [44], causing the back pressure to venous return to be located upstream of the right atrium. With PEEP, the vessels collapsed at higher pressure than normal, that is, there was an increase in P_{CRIT} of these veins, caused by direct mechanical compression by the inflating lungs and/or mechanical compression of intra-abdominal contents, especially the liver [8,44,45]. The compression of the lung and liver of course will have multiple effects, not only changing the time constant (resistance × compliance) for enhancing venous return, but also increasing the resistance and back pressure to blood entering from the portal side into the liver and from the right ventricle into the lung. Therefore, increased pressure within the system can have the venous bed simultaneously change its compliance and resistance, resulting in both a discharging capacitator, and resistive changes that will have

both incremental (flow dependent, ohmic) and fixed back pressure (i.e. P_{CRIT}) resistive components.

Whether this concept is applicable in humans on mechanical ventilation and PEEP, however, is still a matter of debate. While a PEEP-induced collapse of the inferior vena cava in humans is very unlikely due to anatomical reasons, a high collapsibility index of the thoracic part of the superior vena cava was shown [46]. As the part of venous return devoted to superior vena cava flow is close to 25%, a marked and sudden reduction in the size of this vessel has discernible consequences for RV filling. To the contrary, however, no tendency towards collapse could be observed in the surgical patients studied by Jellinek *et al*. [36]. These differences may be readily explained by the volume status of the individual patient. In hemodynamically stable, volume-loaded cardiac surgical patients, increases in Paw up to 20 cmH_2O did not affect venous return and cardiac output, primarily because of an in-phase-associated pressurisation of the abdominal compartment associated with compression of the liver and squeezing of the lungs [47]. Systemic venous return depends on baseline filling status, which will substantially influence the effects of increasing Paw - and thus lung inflation - on SV and cardiac output. This explains that in patients with acute lung injury, baseline RAP was most sensitive in predicting the subsequent hemodynamic depression induced by an apneic positive Paw of 30 cmH_2O [48]. Patients with baseline RAP <10 mmHg demonstrated a more profound hemodynamic depression compared to patients with higher baseline RAP, potentially placing these patients at risk for organ hypo-perfusion. That superior vena cava collapse is related to filling status was recently shown by Vieillard-Baron and coworkers [49], who demonstrated that superior vena cava collapse in septic patients was strongly related to fluid responsiveness.

Right ventricular output

The pumping capability of the right ventricle depends on RV filling volume (preload), RV contractility and the pressure against which the right ventricle ejects, as well as the impedance and compliance of the arterial inflow bed (afterload).

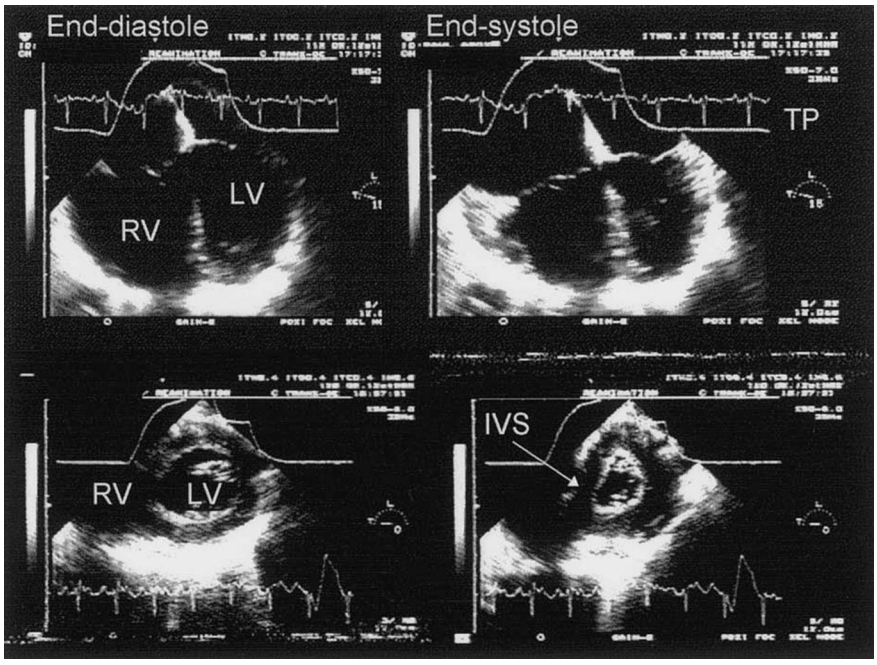
While PEEP decreases RV preload by impairing systemic venous return, it will also increase RV afterload. The exact interaction among RV ejection pressure, pulmonary input impedance and RV systolic function is difficult to define, because RV ejection is more 'continuous' in nature than LV contraction, uses LV contractile force to develop a majority of its intraluminal pressure via the shared muscle fibers of the interventricular septum, and ejects into a vascular system with a highly variable but usually low impedance pulmonary vascular circuit [10,50]. RV afterload can be estimated, however, as maximal RV systolic wall stress [51]. Thus, RV afterload, by the LaPlace equation, is a function of the product of RV end-diastolic volume and RV end-systolic pressure [51]. During ventilation with PEEP, however, exact assessment of these parameters is difficult, because of both the uncertainties when calculating transmural pressures as discussed above and the difficulties in obtaining adequate measurements of RV volumes due to its complex geometry [52]. Increases in pulmonary artery pressure, which is the RV ejection pressure, increases RV afterload, thus impeding RV ejection [52]. If the RV does not empty as much as before, SV will decrease and RV end-systolic volume will increase [51], further increasing RV wall stress, which may result in acute cor pulmonale and cardiovascular collapse. As outlined by Pinsky [10], the pericardium plays an important role in minimizing these potentially detrimental right-sided interactions, markedly limiting RV over-distention. In fact, one of the primary physiological roles of the pericardium is to influence cardiac filling dynamics by exerting external constraining forces over the heart (pericardial constraint), thus preventing the heart from over-dilatation, myocardial hemorrhage, or valvular insufficiency [53].

PEEP can modify pulmonary vascular resistance (PVR), and thus RV afterload, by any of several mechanisms. First, PEEP may reduce PVR by reducing increased pulmonary vasomotor tone due to hypoxic pulmonary vasoconstriction. If PEEP recruits collapsed alveoli, thereby increasing regional alveolar pO_2, hypoxic pulmonary vasoconstriction will be reduced, pulmonary vasomotor tone will fall, and RV ejection will improve [54,55].

Second, PEEP changes PVR by changing lung volume. PVR is related to lung volume in a bimodal fashion, with resistance to flow being minimal near functional residual capacity. As lung volume increases from residual volume to FRC, PVR decreases and vascular capacitance increases. As lung volume continues to increase from FRC to total lung capacity, PVR increases and vascular capacitance decreases. This biphasic behaviour is explained by postulating two different types of intra-parenchymal vessels: intra-alveolar vessels are compressed as lung volume increases, while extra-alveolar vessels are exposed to expanding forces when lung volume increases. At lung volumes below FRC, the effects on extra-alveolar vessels predominate and PVR decreases. As lung volume increases above FRC, effects on intra-alveolar vessels predominate and PVR rises again [56]. At higher lung volumes and Paw, alveolar pressure is elevated relative to pulmonary artery and left atrial pressure [57], which expands zone II regions of the lung [58], where alveolar pressure is the effective pressure against which the right ventricle ejects [41].

Canada and coworkers [59] demonstrated that PVR was U-shaped in both normal and abnormal lungs. Furthermore, they showed that the pulmonary vascular resistance index correlated with oxygen delivery (DO_2), cardiac index and the pulmonary diastolic gradient (pulmonary artery diastolic-left atrial pressure gradient) and with static compliance in normal lungs. The maxima and minima of most variables occurred at

Figure 3



Characteristic echocardiographic patterns of acute cor pulmonale with transesophageal echocardiography. In the upper panel, right ventricular (RV) dilation is observed in a long-axis view, at end-diastole (left) and end-systole (right). Also note the reduced size of the left ventricle (LV). In the lower panel, septal dyskinesia is observed, in the same patient, in a short-axis view: at end-systole/early diastole (right) the interventricular septum (IVS) is shifted toward the LV cavity center, and the septal curvature is inverted (arrow). TP, tracheal pressure. Reproduced from [63], with permission.

a PEEP of 5 cmH_2O in normal lungs and at a PEEP of 10 cmH_2O in abnormal lungs.

In summary, the effects of PEEP on RV output depend on: how PEEP changes lung volume relative to normal FRC; the extent to which it can alleviate hypoxic pulmonary vasoconstriction; and the overall change in pulmonary arterial pressure. Brunet and colleagues [60], for example, demonstrated an inverse correlation between changes in RV function and the increase in mean pulmonary artery pressure. In an ovine model of acute lung injury, Luecke *et al*. [61] found right ventricular end-diastolic volume and right ventricular ejection fraction to be well preserved up to a PEEP of 21 cmH_2O, supporting the findings by Cheatham *et al*. obtained in acute respiratory distress syndrome (ARDS) patients [62]. While these data show that RV dysfunction is not an inevitable result of PEEP, an echocardiographic study from Jardin's group [63] has demonstrated a 25% incidence of acute cor pulmonale due to increased RV outflow impedance in 75 consecutive ARDS patients submitted to protective ventilation (Fig. 3). The same group also provided echocardiographic evidence that the way to set PEEP in ARDS may have significant consequences for RV outflow impedance [64] and that increased RV afterload was the main parameter explaining the decrease in RV SV in ARDS patients [65] . Based on these findings, they strongly recommended RV protection during mechanical ventilation [66] by limitation of PEEP and avoidance of hypercapnic acidosis, which may adversely affect RV performance by inducing pulmonary arteriolar vasoconstriction, leading to pulmonary hypertension [67].

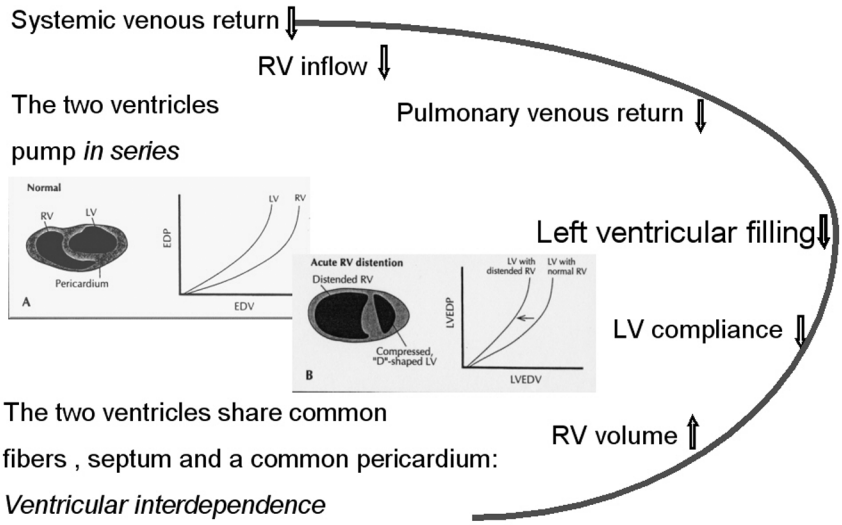
Left ventricular filling and ventricular interdependence

Any decrease in systemic venous return and, thus, RV inflow, must, within a few heart beats, result in decreased pulmonary venous return and inflow to the left ventricle because the two ventricles pump in series. Analogous to systemic venous return, pulmonary venous return to the left ventricle is regulated by the driving pressure, that is, the pressure gradient and the impedance to flow.

In addition to this passive coupling of the right and left ventricle, PEEP may have more direct mechanical effects on LV filling and, thus, on LV preload. PEEP-induced changes in lung volume and, in particular, regional lung volumes constrain the heart in the cardiac fossa.

In addition, because the two ventricles share common fiber bundles, a common interventricular septum, and coexist within the same pericardial space, thus being subjected to pericardial constraint, substantial increases in RV volume must limit LV filling except from severe hypovolemic states. This parallel interaction between the ventricles, whereby the function of one

Figure 4



Effect of positive end-expiratory pressure (PEEP) on left ventricular (LV) filling. Any decrease in systemic venous return and, thus, right ventricular (RV) inflow must result in decreased pulmonary venous return and inflow to the left ventricle because the two ventricles pump in series. In addition to this passive coupling of the right and left ventricle, PEEP may have more direct mechanical effects on LV filling as the two ventricles share common fiber bundles, a common interventricular septum, coexist within the same pericardial space, and are surrounded by a fixed cardiac fossa volume. This parallel interaction between the ventricles, whereby the function of one ventricle influences the function of the other, is called ventricular interdependence. Classically, ventricular interdependence is thought to occur as increases in RV volume decrease LV diastolic compliance, LV preload, and LV output (acute cor pulmonale). EDP, end-diastolic pressure; EDV end-diastolic volume. Inserts adapted from [69], with permission.

ventricle influences the function of the other, is called ventricular interdependence [68,69]. Classically, ventricular interdependence is thought to occur as increases in RV volume decrease LV diastolic compliance, LV preload, and LV output. RV end-diastolic volume increases during spontaneous inspiration, transiently shifting the intra-ventricular septum from its neutral position into the left ventricle [70]. As the right ventricle dilates, LV diastolic compliance is reduced, reducing LV end-diastolic volume (Fig. 4). This may also occur if the application of PEEP results in acute cor pulmonale. However, RV volumes can also decrease during positive-pressure ventilation and PEEP, reducing ventricular interdependence and allowing LV volumes to increase for the same filling pressures [10,71,72]. In addition to shifts of the inter-ventricular septum, increasing ITP may also change the overall shape of the LV cavity due to non-uniformity of changes in cardiac surface pressures [73,74].

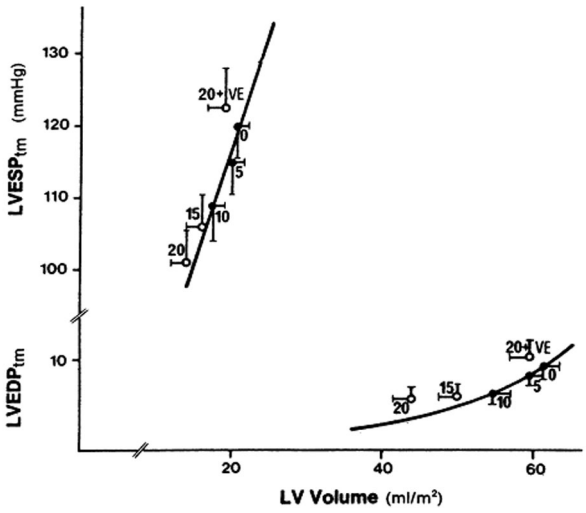
As reviewed by Fessler [41], these factors are difficult to tease apart because of the complex interaction between cardiac and lung volume and the complexity of the in series interactions of the lung and pericardial constraint. In animals, PEEP has been shown to cause flattening of the left ventricle, which is greatest at the free wall [75,76]. In humans, PEEP increased the radius of the curvature of the septum [77-79]. PEEP has been shown in some studies to decrease LV compliance [79,80], which may be due to changes in LV conformation or increased rigidity of the distended surrounding lung [80]. Others have failed to find reduced LV compliance during PEEP [81], or have shown it only when RV dilatation was exaggerated by high levels of PEEP and RV ischemia [82]. In another study [83], the leftward shift of the LV end-diastolic transmural pressure-volume curve observed at high levels of PEEP in patients with ARDS was related to overestimation of transmural pressure rather than to decreased LV diastolic compliance (Fig. 5). Bearing in mind the non-uniformity of cardiac surface pressures, it is difficult to obtain adequate estimates of transmural LV filling pressures at higher levels of PEEP and to assess LV compliance. Therefore, no final conclusions regarding the effect of PEEP on LV compliance can be drawn. Changes in LV conformation induced by PEEP, while of mechanical interest, probably have little impact on cardiac output on PEEP [41,84].

In summary, LV preload during PEEP is predominantly affected by the decrease in systemic venous return and/or the decrease in RV output (series effects), while direct, parallel interactions may have limited effects, unless acute cor pulmonale is present.

Left ventricular output (contractility and afterload)

The pumping capability of the left ventricle depends on LV filling volume (preload), LV contractility and the pressure against which the left venticle ejects (afterload). While PEEP decreases LV preload, its effect on LV contractility probably

Figure 5



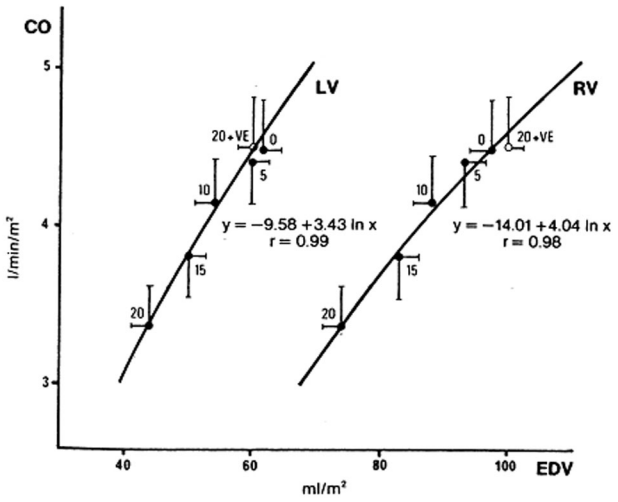
Effects of continuous positive-pressure ventilation on the end-diastolic (ED) and end-systolic (ES) volume (V)-transmural pressure (tm) relationship of the left ventricle (LV). Closed circles represent the mean V-tm coordinates at low levels of positive end-expiratory pressure (PEEP; 0, 5, 10 cmH_2O), and the continuous lines are drawn through these points to indicate typical V-tm curves. Open circles represent the mean V-tm coordinates at high levels of PEEP (15, 20, and 20 cmH_2O) with volume expansion. Both ESV and EDP are reduced at the same pressures, indicating a leftward displacement of the V-tm pressure curves at high levels of PEEP. Reproduced from [83], with permission.

has generated more controversy than any other aspect of heart-lung interactions. This arose in part from difficulty in defining myocardial function, and, once defined, difficulty in measuring it [41]. One commonly used estimate of myocardial function is the Starling relationship; the relationship between filling pressure of a ventricle and mechanical output (SV, cardiac output, work, power). Although this relationship is physiologically relevant, because normal pumping of the ventricles requires that they deliver appropriate amounts of blood to the tissues at acceptably low filling pressures [85], it poses special problems during mechanical ventilation at high ITP: the Starling relationship describes a relationship between ventricular preload and output. Preload is end-diastolic volume and, therefore, a function curve relating end-diastolic volume to mechanical output is a more accurate representation of the Frank-Starling effect. Unfortunately, filling pressures (pulmonary capillary wedge or RAP) are usually more readily available than volume and the inability to accurately measure changes in LV volumes during ventilatory maneuvers still represents a major limitation in the investigations of heart-lung interactions [6,61]. As discussed above, however, these filling pressures are measured relative to ambient pressure and correction for transmural filling pressures is difficult. Therefore, characterisation of ventricular performance in terms of function curves relating filling pressures to output is a 'black box' approach; alterations in diastolic compliance produce effects that are indistinguishable from alterations in contractile performance [85]. Accordingly, a more attractive approach is to examine the relationship between LV end-diastolic volume and cardiac output on PEEP. This has been attempted using numerous techniques [5,61,77,78,81-83,86-88], which, in general, have failed to demonstrate a decrease in LV function (Fig. 6).

The Starling curve slope, however, as well as the most commonly employed clinical indices of ventricular contractile function (e.g., ejection fraction, shortening velocity, fractional area shortening) are affected by changing external loading conditions [85]. Therefore, as an alternative to characterisation of systolic function in terms of stress and shortening, Suga and Sagawa proposed an elastance approach, that is, the analysis of end-systolic pressure-volume relationships (ESPVRs) [89,90]. Briefly, instantaneous pressure-volume diagrams of consecutive cardiac cycles are recorded while changing loading conditions and the point of maximal elastance (pressue/volume) is measured from each beat (termed Emax). The parameters of that line, its slope and its intercept, can be used to define myocardial contractility [41]. Despite the fact that subsequent studies could not confirm the initially proposed load-independence and linearity of the ESPVR [91], the ESPVR has proven to be a useful conceptual approach to assessment of contractile function [85]. While the problem of assessing transmural pressures during PEEP still exists, errors in estimating cardiac surface pressures would be more likely to affect the intercept of an ESPV curve, rather than its slope [41]. In animal studies [87,92], the slope of the ESPVR is not altered by PEEP, which supports the conclusion that contractility is unchanged.

In contrast to its effect on the right ventricle, PEEP has been shown to decrease LV afterload. PEEP increases the pressure around structures in the thorax and, to a lesser extent, in the abdominal cavity, relative to atmospheric pressure. Because the rest of the circulation is at atmospheric pressure, this results in a pressure differential, with most of the systemic circulation being under lower pressure than the left ventricle and the thoracic aorta [18]. Thus, increased ITP, at constant arterial pressure, decreases the force necessary to eject blood from the left ventricle in a manner exactly analogous to decreased arterial pressure, at constant ITP [93-95]. Again, however, problems arise with the concept of ITP and the exact calculation of effective transmural pressure: in these studies, LV afterload was measured as LV end-systolic transmural pressure, calculated as LV end-systolic cavitary minus Pes. This assumes that Pes represents cardiac surface pressure. Although this is a common assumption, when the pericardium is intact, changes in cardiac volume may render this assumption invalid [96]. When the heart is small, changes in ITP are transmitted to the cardiac surface and the effect of pericardial elasticity on cardiac surface pressure is small. On the other hand, with

Figure 6



Starling relationship between cardiac output (CO) and the end-diastolic volume (EDV) of the right ventricle (RV; right curve) and left ventricle (LV; left curve) as airway pressure was progressively increased from 0 (upper right data point) to 20 cmH_2O (lower left data point). Note that volume expansion at a positive end-expiratory pressure (PEEP) of 20 cmH_2O (20 + VE) entirely reversed the decrease in RV EDV and LV EDV and restored CO. VE, volume expansion. Reproduced from [83], with permission.

cardiac dilatation, the elasticity of the pericardium becomes greater and may have greater effects on LV surface pressure. This is because cardiac surface pressure is the arithmetic sum of ITP and pericardial elastic pressure. As the heart becomes larger, pericardial elastic pressure becomes an increasingly important component of cardiac surface pressure during PEEP [97]. This means that changes in Pes may not be a good indicator of cardiac surface pressure when the heart is dilated and may result in inaccurate overestimations of LV transmural pressure [96]. Therefore, it is difficult to assess whether the PEEP-induced afterload reduction is actually due to a reduction in LV end-systolic transmural pressure or simply related to the commonly observed decrease in mean arterial pressure.

Whatever the major component of PEEP-induced reduction in LV afterload may be, that decrease in afterload usually does not translate into increased cardiac output, as the adverse effects on LV filling usually predominate. The failing heart, however, is more sensitive to decreased afterload. As patients with congestive heart failure (CHF) are usually hypervolemic, they are also less sensitive to decreased preload [98]. Therefore, in a manner analogous to the effects of vasodilators in CHF, cardiac output could rise when PEEP is applied to patients with poor myocardial function [96]. Besides these direct mechanical effects, however, the beneficial effects of PEEP in these patients may also be mediated by poorly understood reflex vasodilation and alterations in sympathoadrenal function, thereby profoundly affecting the coupling between central and peripheral circulation [99]. While positive pressure ventilation and continuous positive airway pressure (CPAP) are advocated as adjunctive mode of therapy in patients with acute pulmonary edema and CHF [100,101], some words of caution are warranted. First, mechanical ventilation with PEEP is often considered to be equivalent to CPAP. However, with mechanical ventilation with PEEP, ITP is increased throughout all phases of the respiratory cycle, while with CPAP, ITP is increased at end-expiration, but decreases during inspiration. Thus, the venous return effects of PEEP are greater than those with CPAP [96]. Second, CPAP in patients with CHF, especially in those with concomitant obstructive sleep apnea, will exert much of its beneficial effects by reducing the elevation of sympathetic tone, thus affecting autonomic function rather than ventricular loading. This will not hold true for the deeply sedated critically ill patient with myocardial ischemia ventilated with high levels of PEEP for ARDS. Third, increasing cardiac surface pressure could lead to a decrease in coronary blood flow because of increased epicardial surface pressure and/or increased RAP. Tucker and Murray [102], for example, reported decreases in myocardial blood flow out of proportion to decreases in myocardial work, suggesting that if PEEP led to decreases in coronary blood flow out of proportion to metabolic needs, PEEP actually could be dangerous when coronary flow reserve was limited, as in coronary artery disease. Although the final word is far from being spoken, some caution is warranted in treating patients with active ischemic heart disease with high levels of PEEP [96].

Besides patients with CHF and cardiogenic pulmonary edema, those patients with chronic obstructive pulmonary disease (COPD) may represent a second group of patients where application of CPAP and PEEP actually can be beneficial. In 1988, Lemaire and coworkers [103] reported that patients with severe COPD but adequate ventilatory parameters for weaning often went into severe cardiogenic pulmonary edema during the weaning trial. Following diuresis and improvement in cardiovascular reserve, however, these patients could be successfully weaned from the ventilatory support. Richard *et al.* [104] examined 12 ventilator dependent patients with COPD during their weaning trials. They demonstrated a reduction in LV ejection fraction in patients during the T-piece trial, but no change in LV ejection fraction in the same patients when supported by 10 cmH_2O of pressure support ventilation.

In these patients with severe COPD, externally applied PEEP is useful to counteract the possible presence of intrinsic PEEP. External PEEP reduces the ITP swings especially during spontaneous ventilation, thus reducing cardiac overload. Thus, application of PEEP even in these patients can be extremely beneficial from a hemodynamic point of view.

Hemodynamic effects of PEEP in patients with acute lung injury and ARDS

In this review, we cannot discuss in detail all the possible interactions between the application of different levels of PEEP or mean Paw on hemodynamics in patients with acute lung injury (ALI)/ARDS. However, we will try to briefly focus on the relationships between the hemodynamic response to PEEP or mean Paw and lung morphology, chest wall elastance and intra-abdominal pressure (IAP). The ARDS lung is characterized by diffuse, increased permeability and edema increases equally at each lung level, as a sponge filled by water. The increased lung mass causes not only compression of the most dependent alveoli, due to the increased weight of the levels above in a gravitational field, but also of the pulmonary vessels [105]. Other factors influencing the changes in the properties of the pulmonary vessels in ALI/ARDS are the alterations in the endothelial cells [106] and vascular microthrobosis [107]. The morphology of the ARDS lung is extremely inhomogeneous and it is likely that the effects on hemodynamics can be markedly influenced by this inhomogeneity of alveolar gas distribution at different levels of PEEP and mean Paw. Several studies showed that in patients in which the application of PEEP determined effective alveolar recruitment, mean pulmonary artery pressure decreases with Paw application [108], while cardiac output is not severely affected. This is due to the fact that alveolar recruitment is paralleled by a simultaneous recruitment of pulmonary vessels with a subsequent increase in the pulmonary vascular volume. This favours an improvement of the RV and consequently LV function, minimizing the possible negative effects on hemodynamics. Thus, the predictability of alveolar recruitment can be extremely important for predicting the hemodynamic response to PEEP. Several factors should be considered: the lung morphology, which can be evaluated by CT scan and chest X-ray; the etiology of the disease; and the effective recruitment measured by mechanics or by the effect on gas-exchange. Computed tomography showed that in the majority of the patients with ARDS, densities are located in the most dependent part of the lung in the supine position, leaving the non-dependent part relatively well aerated [13]. Rouby and colleagues [109,110] showed that the morphological aspects of the lung parenchyma can be markedly different between patients. The patients were classified as having a 'lobar' pattern if areas of lung attenuation had a lobar or segmental distribution, a 'diffuse' pattern if lung attenuation was diffusely distributed throughout the lungs, or a 'patchy' pattern if there were lobar or segmental areas of lung attenuation in some parts of the lungs but without recognized anatomical limits in others. Patients with lobar densities on CT were much less recruitable at high PEEP levels compared to patients with patchy-lobar or diffuse densities. Thus, CT scans are useful for evaluating regional distribution of disease, the nature of the infiltrates, and the potential for recruitment. In recent years, a number of studies have identified differences between pulmonary (ARDSp) and extrapulmonary (ARDSexp) ARDS in terms of morphology [111], respiratory mechanics and response to recruitment [112]. In fact, the potential for recruitment is higher in the presence of alveolar collapse and lower if alveolar consolidation predominates. Gattinoni and colleagues [112] found that an increase of PEEP leads to opposite effects on elastance: in ARDSp, increasing PEEP caused an increase of the elastance of the total respiratory system due to an increase in lung elastance with no change in chest wall elastance. Conversely, in ARDSexp the application of PEEP caused a reduction of the elastance of the total respiratory system, mainly due to a reduction in lung elastance and chest wall elastance. Moreover, although an increase in PEEP led to an elevation of end-expiratory lung volume in both ARDSp and ARDSexp, it resulted in alveolar recruitment primarily in ARDSexp. Thus, etiology is an important predictor of potential recruitment with PEEP and mean Paw.

Another important factor to be considered is the IAP. Several studies showed that IAP is increased in the majority of critically ill patients [113,114]. We showed that an IAP higher than 12 mmHg can markedly affect chest wall elastance [112]. Thus, it is likely that application of PEEP in patients with IAP higher than 12 mmHg can produce more deleterious effects on hemodynamics, as shown in ARDS patients [115].

We propose an integrated approach to optimize PEEP and mean Paw during mechanical ventilation in ALI/ARDS to minimize the possible negative hemodynamic effects by evaluating lung morphology using chest radiography and CT scans, IAP, the etiology of ARDS, and the response to PEEP/mean Paw.

Chest radiography should be performed first of all. If lobar characteristics are present, poor response to increased mean Paw in terms of recruitment can be expected. In contrast, patchy or diffuse injury on chest radiography cannot predict the response to increased mean Paw. In this case, we suggest that a CT scan is done to evaluate the distribution of the disease. The CT scan should be performed at two different mean Paws (increasing PEEP) to evaluate the potential for recruitment. Second, we suggest measuring IAP by using the bladder pressure technique [116]. If IAP is lower than 12 mmHg, Paw likely reflects the real transpulmonary pressure, as the elastance of the chest wall probably is within normal limits. If the IAP is greater than 12 mmHg, the mechanical properties of the chest wall are likely to be altered [112]. Thus, Paw should be titrated considering that at least 30% to 70% of the Paw is lost to inflate the chest wall and not the lung [117]. Third, the etiology of ARDS should be considered in this setting. Ventilator-associated pneumonia is less likely to respond to increased Paw than community acquired pneumonia and ARDSexp. Fourth, a PEEP trial based on oxygenation, arterial carbon dioxide partial pressure (PaCO2) and respiratory mechanics should be performed

[118,119] as proposed by Bohm and Lachmann [120] and recently investigated in animal [121] and human studies [122]. It consists of a first part to open up the lung (increasing plateau and PEEP levels), and a second part to keep the lung open (progressively decreasing the PEEP levels). Recruitment can be easily evaluated at the bedside by the oxygenation response, while over-distension is likely if PaCO2 increases and compliance of the respiratory system decreases. Oxygenation has been found to correlate with recruitment in several experimental [121,123] and clinical studies [2,124]. On the other hand, an increase in PaCO2 and reduction in compliance of the respiratory system likely indicate overstretching of the alveolar units associated with an increase in dead space [118].

Thus, in ALI/ARDS a higher risk of potential negative effects from the application of PEEP or mean Paw on hemodynamics should be expected in patients with poor recruitment and increased IAP, that is, high chest wall elastance. On the other hand, less negative effects should be expected in patients with more potential of recruitment and low IAP, that is, low chest wall elastance.

How to assess the effects of PEEP on circulatory function in the ICU?

Summarizing the complex effects of PEEP on cardiocirculatory function, the most important facts to keep in mind at the bedside are the potentially detrimental consequences for venous return and RV afterload. As these effects are ultimately mediated by increased lung volumes, leading to potential alveolar over-distention, one should be aware that ventilator-associated lung injury due to high lung volumes can, at the same time, result in 'ventilator-associated heart injury'. Therefore, monitoring lung volumes would be a major component to limit adverse hemodynamic effects, but unfortunately is not feasible to date. By monitoring the hemodynamic effects of individual PEEP settings, however, one can make some inferences on resulting lung volume changes. In light of the ongoing debate on the mechanism of alveolar derecruitment (alveolar collapse versus alveolar flooding), rendering the use of high levels of PEEP as ventilatory strategy in ARDS questionable [125], precise assessment of the hemodynamic changes induced by mechanical ventilation in the individual patient may help in the selection of the right level of PEEP. Measurement of cardiac or intrathoracic volumes has been shown to be clearly superior to filling pressures with regard to cardiac preload assessment during mechanical ventilation with PEEP [61,62,126-129]. Combined with continuous cardiac output measurements using the rapid-response thermodilution technique and/or pulse contour-derived techniques [130,131], volume-based techniques can be regarded as state of the art monitoring of cardiac function during ventilation with PEEP. In addition, echocardiography can be a powerful tool to assess RV function, especially if acute cor pulmonale is a concern [63,132,133], as well as to estimate LV function [134-136].

Competing interests

The author(s) declare that they have no competing interests.

References

1. Dreyfuss D, Saumon G: **Ventilator-induced lung injury. Lessons from experimental studies.** *Am J Respir Crit Care Med* 1998, **157:**294-330.
2. Maggiore SM, Jonson B, Richard JC, Jaber S, Lemaire F, Brochard L: **Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance.** *Am J Respir Crit Care Med* 2001, **164:**795-801.
3. Rouby JJ, Lu Q, Goldstein I: **Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome**. *Am J Respir Crit Care Med* 2002, **165:**1182-1186.
4. Cournand A, Motley HL, Werko L, Richards D: **Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man.** *Am J Physiol* 1948, **152:**162-174.
5. Viquerat CE, Righetti A, Suter PM: **Biventricular volumes and function in patients with adult respiratory distress syndrome ventilated with PEEP.** *Chest* 1983, **83:**509-514.
6. Pinsky M: **The hemodynamic consequences of mechanical ventilation: an evolving story.** *Int Care Med* 1997, **23:**493-503.
7. Robotham JL, Peters J, Takata M: **Cardiorespiratory interactions.** In *Pulmonary and Critical Care Medicine*. *Vol 3*. St Louis: Mosby-Year Book; 1993:1-25.
8. Scharf S: **Ventilatory support in cardiac failure.** In *The Ill Cardiac Patient*. Edited by Kvetan V, Dantzker DR. Philadelphia: Lippincott-Raven; 1996:29-45.
9. Romand JA, Shi W, Pinsky MR: **Cardiopulmonary effects of positive pressure ventilation during acute lung injury.** *Chest* 1995, **108:**1041-1048.
10. Pinsky M: **Hemodynamic effects of ventilation and ventilatory maneuvers.** In *Respiratory-Circulatory Interactions in Health and Disease*. Edited by Scharf SM, Pinsky MR, Magder S. New York: Marcel Dekker, Inc.; 2001:183-218.
11. O'Quin RJ, Marini JJ, Culver BH, Butler J: **Transmission of airway pressure to pleural space during lung edema and chest wall restriction.** *J Appl Physiol* 1985, **59:**1171-1177.
12. Novak R, Matuschak GM, Pinsky MR: **Effect of positive-pressure ventilatory frequency on regional pleural pressure.** *J Appl Physiol* 1988, **65:**1314-1323.
13. Gattinoni L, Mascheroni D, Torresin A, Marcolin R, Fumagalli R, Vesconi S, Rossi GP, Rossi F, Baglioni S, Bassi F, *et al.*: **Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study.** *Intensive Care Med* 1986, **12:**137-142.
14. Scharf SM, Ingram RH Jr: **Effects of decreasing lung compliance with oleic acid on the cardiovascular response to PEEP.** *Am J Physiol* 1977, **233:**H635-641.
15. Pinsky M, Vincent JL, De Smet JM: **Estimating left ventricular filling pressure during positive end-expiratory pressure in humans.** *Am Rev Respir Dis* 1991, **143:**25-31.
16. Kingma I, Smiseth OA, Frais MA, Smith ER, Tyberg JV: **Left ventricular external constraint: relationship between pericardial, pleural and esophageal pressures during positive end-expiratory pressure and volume loading in dogs.** *Ann Biomed Eng* 1987, **15:**331-346.
17. O'Quin R, Marini JJ: **Pulmonary artery occlusion pressure: clinical physiology, measurement, and interpretation.** *Am Rev Respir Dis* 1983, **128:**319-326.
18. Klinger J: **Hemodynamics and positive end-expiratory pressure in critically ill patients.** *Crit Care Clinics North Am* 1996, **12:**841-864.
19. Chapin JC, Downs JB, Douglas ME, Murphy EJ, Ruiz BC: **Lung expansion, airway pressure transmission, and positive end-expiratory pressure.** *Arch Surg* 1979, **114:**1193-1197.
20. Mirro R, Busija D, Green R, Leffler C: **Relationship between mean airway pressure, cardiac output, and organ blood flow with normal and decreased respiratory compliance.** *J Pediatr* 1987, **111:**101-106.
21. Magder S, Scharf S: **Venous return.** In *Respiratory-Circulatory Interactions in Health and Disease.* Edited by Scharf SM, Pinsky MR, Magder S. New York: Marcel Dekker, Inc.; 2001:93-112.

22. Guyton AC: **Determination of cardiac output by equating venous return curves cardiac response curves.** *Physiol Rev* 1955, **35:**123-129.
23. Guyton AC, Lindsey AW, Abernathy B, Richardson T: **Venous return at various right atrial pressures and the normal venous return curve.** *Am J Physiol* 1957, **189:**609-615.
24. Robotham JL, Peters J: **Mechanical effects of intrathoracic pressure on ventricular performance.** In *Heart-Lung Interactions in Health and Disease. Vol 46*. Edited by Scharf SM. New York: Marcel Dekker Inc.; 1989:251-283.
25. Pinsky M: **Instantaneous venous return curves in intact canine preparation.** *J Appl Physiol* 1984, **56:**765-771.
26. Goldberg HS, Rabson J: **Control of cardiac output by systemic vessels. Circulatory adjustments to acute and chronic respiratory failure and the effect of therapeutic interventions.** *Am J Cardiol* 1981, **47:**696-702.
27. Fessler HE, Permutt S: **Interaction between the circulatory and ventilatory pumps.** In *The Thorax*. Edited by Roussos C. New York: Marcel Dekker, Inc.; 1995:1621-1640.
28. Pinsky MR: **Determinants of pulmonary arterial flow variation during respiration.** *J Appl Physiol* 1984, **56:**1237-1245.
29. Pinsky MR: **Instantaneous venous return curves in an intact canine preparation.** *J Appl Physiol* 1984, **56:**765-771.
30. Guntheroth WG, Gould R, Butler J, Kinnen E: **Pulsatile flow in pulmonary artery, capillary, and vein in the dog.** *Cardiovasc Res* 1974, **8:**330-337.
31. Chevalier PA, Weber KC, Engle JC, Gerasch DA, Fox IJ: **Direct measurements of right and left heart outputs in a Valsalva-like maneuver in dogs.** *Proc Soc Exp Biol Med* 1972, **139:** 1429-1437.
32. Scharf SM, Brown R, Saunders N, Green LH: **Hemodynamic effects of positive-pressure inflation.** *J Appl Physiol* 1980, **49:** 124-131.
33. Scharf SM, Caldini P, Ingram RH Jr: **Cardiovascular effects of increasing airway pressure in the dog.** *Am J Physiol* 1977, **232:**H35-43.
34. Fessler HE, Brower RG, Wise RA, Permutt S: **Effects of positive end-expiratory pressure on the gradient for venous return.** *Am Rev Respir Dis* 1991, **143:**19-24.
35. Nanas S, Magder S: **Adaptations of the peripheral circulation to PEEP.** *Am Rev Respir Dis* 1992, **146:**688-693.
36. Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD: **Influence of positive airway pressure on the pressure gradient for venous return in humans.** *J Appl Physiol* 2000, **88:** 926-932.
37. Hamilton DR, Dani RS, Semlacher RA, Smith ER, Kieser TM, Tyberg JV: **Right atrial and right ventricular transmural pressures in dogs and humans. Effects of the pericardium.** *Circulation* 1994, **90:**2492-2500.
38. Tyberg JV, Taichman GC, Smith ER, Douglas NW, Smiseth OA, Keon WJ: **The relationship between pericardial pressure and right atrial pressure: an intraoperative study.** *Circulation* 1986, **73:**428-432.
39. Pinsky MR, Desmet JM, Vincent JL: **Effect of positive end-expiratory pressure on right ventricular function in humans.** *Am Rev Respir Dis* 1992, **146:**681-687.
40. Permutt S, Bromberger-Barnea B, Bane HN: **Alveolar pressure, pulmonary venous pressure, and the vascular waterfall.** *Med Thorac* 1962, **19:**239-260.
41. Fessler HE: **Mechanical ventilation with PEEP.** In *Respiratory-Circulatory Interactions in Health and Disease*. Edited by Scharf SM, Pinsky MR, Magder S. New York: Marcel Dekker, Inc.; 2001: 807-835.
42. Fessler HE, Brower RG, Shapiro EP, Permutt S: **Effects of positive end-expiratory pressure and body position on pressure in the thoracic great veins.** *Am Rev Respir Dis* 1993, **148:**1657-1664.
43. Permutt S, Riley RL: **Hemodynamics of collapsible vessels with tone: the vascular waterfall.** *J Appl Physiol* 1963, **18:**924-932.
44. Takata M, Wise RA, Robotham JL: **Effects of abdominal pressure on venous return: abdominal vascular zone conditions.** *J Appl Physiol* 1990, **69:**1961-1972.
45. Moreno AH, Burchell AR, Van der Woude R, Burke JH: **Respiratory regulation of splanchnic and systemic venous return.** *Am J Physiol* 1967, **213:**455-465.
46. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F: **Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support.** *Anesthesiology* 2001, **95:**1083-1088.
47. van den Berg PC, Jansen JR, Pinsky MR: **Effect of positive pressure on venous return in volume-loaded cardiac surgical patients.** *J Appl Physiol* 2002, **92:**1223-1231.
48. Jellinek H, Krafft P, Fitzgerald RD, Schwarz S, Pinsky MR: **Right atrial pressure predicts hemodynamic response to apneic positive airway pressure.** *Crit Care Med* 2000, **28:**672-678.
49. Vieillard-Baron A, Chergui K, Rabiller A, Peyrouset O, Page B, Beauchet A, Jardin F: **Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients.** *Intensive Care Med* 2004, **30:**1734-1739.
50. Mebazaa A, Karpati P, Renaud E, Algotsson L: **Acute right ventricular failure - from pathophysiology to new treatments.** *Intensive Care Med* 2004, **30:**185-196.
51. Maughan WL, Shoukas AA, Sagawa K, Weisfeldt ML: **Instantaneous pressure-volume relationship of the canine right ventricle.** *Circ Res* 1979, **44:**309-315.
52. Tulevski II, Romkes H, Dodge-Khatami A, van der Wall EE, Groenink M, van Veldhuisen DJ, Mulder BJ: **Quantitative assessment of the pressure and volume overloaded right ventricle: imaging is a real challenge.** *Int J Cardiovasc Imaging* 2002, **18:** 41-51.
53. Takata M, Robotham JL: **Mechanical heart-pericardium-lung interactions.** In *Respiratory-Circulatory Interactions in Health and Disease.* Edited by Scharf SM, Pinsky MR, Magder S. New York: Marcel Dekker, Inc.; 2001:257-278.
54. Marshall BE, Marshall C, Frasch F, Hanson CW: **Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 1. Physiologic concepts.** *Intensive Care Med* 1994, **20:**291-297.
55. Marshall BE, Hanson CW, Frasch F, Marshall C: **Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 2. Pathophysiology**. *Intensive Care Med* 1994, **20:**379-389.
56. Burton AC, Patel DJ: **Effect on pulmonary vascular resistance of inflation of the rabbit lungs.** *J Appl Physiol* 1958, **12:**239-246.
57. Whittenberger JL, Mc GM, Berglund E, Borst HG: **Influence of state of inflation of the lung on pulmonary vascular resistance.** *J Appl Physiol* 1960, **15:**878-882.
58. West JB, Dollery CT, Naimark A: **Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures.** *J Appl Physiol* 1964, **19:**713-724.
59. Canada E, Benumof JL, Tousdale FR: **Pulmonary vascular resistance correlates in intact normal and abnormal canine lungs.** *Crit Care Med* 1982, **10:**719-723.
60. Brunet F, Dhainaut JF, Devaux JY, Huyghebaert MF, Villemant D, Monsallier JF: **Right ventricular performance in patients with acute respiratory failure.** *Intensive Care Med* 1988, **14(Suppl 2):**474-477.
61. Luecke T, Roth H, Herrmann P, Joachim A, Weisser G, Pelosi P, Quintel M: **Assessment of cardiac preload and left ventricular function under increasing levels of positive end-expiratory pressure.** *Intensive Care Med* 2004, **30:**119-126.
62. Cheatham ML, Nelson LD, Chang MC, Safcsak K: **Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure.** *Crit Care Med* 1998, **26:**1801-1806.
63. Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, Beauchet A, Jardin F: **Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis.** *Crit Care Med* 2001, **29:**1551-1555.
64. Schmitt JM, Vieillard-Baron A, Augarde R, Prin S, Page B, Jardin F: **Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements.** *Crit Care Med* 2001, **29:**1154-1158.
65. Vieillard-Baron A, Loubieres Y, Schmitt JM, Page B, Dubourg O, Jardin F: **Cyclic changes in right ventricular output impedance during mechanical ventilation.** *J Appl Physiol* 1999, **87:**1644-1650.
66. Vieillard-Baron A, Jardin F: **Why protect the right ventricle in patients with acute respiratory distress syndrome?** *Curr Opin Crit Care* 2003, **9:**15-21.

67. Viitanen A, Salmenpera M, Heinonen J: **Right ventricular response to hypercarbia after cardiac surgery.** *Anesthesiology* 1990, **73:**393-400.
68. Scharf SM, Brown R: **Influence of the right ventricle on canine left ventricular function with PEEP.** *J Appl Physiol* 1982, **52:** 254-259.
69. Weber KT, Janicki JS, Shroff S, Fishman AP: **Contractile mechanics and interaction of the right and left ventricles.** *Am J Cardiol* 1981, **47:**686-695.
70. Brinker JA, Weiss JL, Lappe DL, Rabson JL, Summer WR, Permutt S, Weisfeldt ML: **Leftward septal displacement during right ventricular loading in man.** *Circulation* 1980, **61:**626-633.
71. Janicki JS, Weber KT: **The pericardium and ventricular interaction, distensibility, and function.** *Am J Physiol* 1980, **238:**H494-503.
72. Olsen CO, Tyson GS, Maier GW, Spratt JA, Davis JW, Rankin JS: **Dynamic ventricular interaction in the conscious dog.** *Circ Res* 1983, **52:**85-104.
73. Santamore WP, Bove AA, Heckman JL: **Right and left ventricular pressure-volume response to positive end-expiratory pressure.** *Am J Physiol* 1984, **246:**H114-119.
74. Cassidy SS, Schwiep F: **Cardiovascular effects of positive end-expiratory pressure.** In *Heart-Lung Interactions in Health and Disease. Vol 46*. Edited by Scharf SM. New York: Marcel Dekker Inc.; 1989:463-506.
75. Cassidy SS, Mitchell JH, Johnson RL Jr: **Dimensional analysis of right and left ventricles during positive-pressure ventilation in dogs.** *Am J Physiol* 1982, **242:**H549-556.
76. Cassidy SS, Ramanathan M: **Dimensional analysis of the left ventricle during PEEP: relative septal and lateral wall displacements.** *Am J Physiol* 1984, **246:**H792-805.
77. Cassidy SS, Eschenbacher WL, Robertson CH Jr, Nixon JV, Blomqvist G, Johnson RL Jr: **Cardiovascular effects of positive-pressure ventilation in normal subjects.** *J Appl Physiol* 1979, **47:**453-461.
78. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP: **Influence of positive end-expiratory pressure on left ventricular performance.** *N Engl J Med* 1981, **304:**387-392.
79. Haynes JB, Carson SD, Whitney WP, Zerbe GO, Hyers TM, Steele P: **Positive end-expiratory pressure shifts left ventricular diastolic pressure-area curves.** *J Appl Physiol* 1980, **48:** 670-676.
80. Lloyd TC Jr: **Mechanical cardiopulmonary interdependence.** *J Appl Physiol* 1982, **52:**333-339.
81. Fewell JE, Abendschein DR, Carlson CJ, Rapaport E, Murray JF: **Continuous positive-pressure ventilation does not alter ventricular pressure-volume relationship.** *Am J Physiol* 1981, **240:** H821-826.
82. Schulman DS, Biondi JW, Zohgbi S, Cecchetti A, Zaret BL, Soufer R: **Left ventricular diastolic function during positive end-expiratory pressure. Impact of right ventricular ischemia and ventricular interaction.** *Am Rev Respir Dis* 1992, **145:**515-521.
83. Dhainaut JF, Devaux JY, Monsallier JF, Brunet F, Villemant D, Huyghebaert MF: **Mechanisms of decreased left ventricular preload during continuous positive pressure ventilation in ARDS.** *Chest* 1986, **90:**74-80.
84. Veddeng OJ, Myhre ES, Risoe C, Smiseth OA: **Selective positive end-expiratory pressure and intracardiac dimensions in dogs.** *J Appl Physiol* 1992, **73:**2016-2020.
85. LeWinter MM, Osol G: **Normal physiology of the cardiovascular system.** In *Hurst´s The Heart*. 10th edition. Edited by Fuster V, Alexander RW, O´Rouke RA. New York: McGraw-Hill; 2001:63-98.
86. Huemer G, Kolev N, Kurz A, Zimpfer M: **Influence of positive end-expiratory pressure on right and left ventricular performance assessed by Doppler two-dimensional echocardiography.** *Chest* 1994, **106:**67-73.
87. Johnston WE, Vinten-Johansen J, Santamore WP, Case LD, Little WC: **Mechanism of reduced cardiac output during positive end-expiratory pressure in the dog.** *Am Rev Respir Dis* 1989, **140:**1257-1264.
88. Berglund JE, Halden E, Jakobson S, Landelius J: **Echocardiographic analysis of cardiac function during high PEEP ventilation.** *Intensive Care Med* 1994, **20:**174-180.
89. Suga H, Sagawa K, Shoukas AA: **Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio.** *Circ Res* 1973, **32:**314-322.
90. Sagawa K: **The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use.** *Circulation* 1981, **63:**1223-1227.
91. Kass DA, Maughan WL: **From 'Emax' to pressure-volume relations: a broader view.** *Circulation* 1988, **77:**1203-1212.
92. Crottogini AJ, Willshaw P, Barra JG, Breitbart GJ, Pichel RH: **End-systolic pressure-volume relationships in dogs during ventilation with PEEP.** *Am J Physiol* 1988, **254:**H664-670.
93. Fessler HE, Brower RG, Wise RA, Permutt S: **Effects of systolic and diastolic positive pleural pressure pulses with altered cardiac contractility.** *J Appl Physiol* 1992, **73:**498-505.
94. Pinsky MR, Matuschak GM, Klain M: **Determinants of cardiac augmentation by elevations in intrathoracic pressure.** *J Appl Physiol* 1985, **58:**1189-1198.
95. Pinsky MR, Summer WR, Wise RA, Permutt S, Bromberger-Barnea B: **Augmentation of cardiac function by elevation of intrathoracic pressure.** *J Appl Physiol* 1983, **54:**950-955.
96. Scharf S: **Ventilatory support in the failing heart.** In *Respiratory-Circulatory Interactions in Health and Disease.* Edited by Scharf SM, Pinsky MR, Magder S. New York: Marcel Dekker, Inc.; 2001: 519-550.
97. Takata M, Robotham JL: **Ventricular external constraint by the lung and pericardium during positive end-expiratory pressure.** *Am Rev Respir Dis* 1991, **143:**872-875.
98. Pouleur H, Covell JW, Ross J Jr: **Effects of nitroprusside on venous return and central blood volume in the absence and presence of acute heart failure.** *Circulation* 1980, **61:**328-337.
99. Genovese J, Huberfeld S, Tarasiuk A, Moskowitz M, Scharf SM: **Effects of CPAP on cardiac output in pigs with pacing-induced congestive heart failure.** *Am J Respir Crit Care Med* 1995, **152:** 1847-1853.
100. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD: **Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea.** *N Engl J Med* 2003, **348:**1233-1241.
101. Nadar S, Prasad N, Taylor RS, Lip GY: **Positive pressure ventilation in the management of acute and chronic cardiac failure: a systematic review and meta-analysis.** *Int J Cardiol* 2005, **99:** 171-185.
102. Tucker HJ, Murray JF: **Effects of end-expiratory pressure on organ blood flow in normal and diseased dogs.** *J Appl Physiol* 1973, **34:**573-577.
103. Lemaire F, Teboul JL, Cinotti L, Giotto G, Abrouk F, Steg G, Macquin-Mavier I, Zapol WM: **Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation.** *Anesthesiology* 1988, **69:**171-179.
104. Richard C, Teboul JL, Archambaud F, Hebert JL, Michaut P, Auzepy P: **Left ventricular function during weaning of patients with chronic obstructive pulmonary disease.** *Intensive Care Med* 1994, **20:**181-186.
105. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L: **Vertical gradient of regional lung inflation in adult respiratory distress syndrome.** *Am J Respir Crit Care Med* 1994, **149:**8-13.
106. Orfanos SE, Mavrommati I, Korovesi I, Roussos C: **Pulmonary endothelium in acute lung injury: from basic science to the critically ill.** *Intensive Care Med* 2004, **30:**1702-1714.
107. Vesconi S, Rossi GP, Pesenti A, Fumagalli R, Gattinoni L: **Pulmonary microthrombosis in severe adult respiratory distress syndrome.** *Crit Care Med* 1988, **16:**111-113.
108. Gattinoni L, Pesenti A, Baglioni S, Vitale G, Rivolta M, Pelosi P: **Inflammatory pulmonary edema and positive end-expiratory pressure: correlations between imaging and physiologic studies.** *J Thorac Imaging* 1988, **3:**59-64.
109. Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ: **Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Adult Respiratory Distress Syndrome.** *Intensive Care Med* 2000, **26:**1215-1227.
110. Rouby JJ, Puybasset L, Cluzel P, Richecoeur J, Lu Q, Grenier P: **Regional distribution of gas and tissue in acute respiratory distress syndrome. II. Physiological correlations and definition of an ARDS Severity Score. CT Scan ARDS Study Group.** *Intensive Care Med* 2000, **26:**1046-1056.

111. Gattinoni L, Caironi P, Pelosi P, Goodman LR: **What has computed tomography taught us about the acute respiratory distress syndrome?** *Am J Respir Crit Care Med* 2001, **164:** 1701-1711.
112. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A: **Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes?** *Am J Respir Crit Care Med* 1998, **158:**3-11.
113. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, Del Turco M, Wilmer A, Brienza N, Malcangi V, *et al.*: **Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study.** *Crit Care Med* 2005, **33:**315-322.
114. Malbrain ML, Chiumello D, Pelosi P, Wilmer A, Brienza N, Malcangi V, Bihari D, Innes R, Cohen J, Singer P, *et al.*: **Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study.** *Intensive Care Med* 2004, **30:** 822-829.
115. Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V: **Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy.** *Anesthesiology* 2002, **96:**795-802.
116. Iberti TJ, Lieber CE, Benjamin E: **Determination of intra-abdominal pressure using a transurethral bladder catheter: clinical validation of the technique.** *Anesthesiology* 1989, **70:**47-50.
117. Gattinoni L, Carlesso E, Valenza F, Chiumello D, Caspani ML: **Acute respiratory distress syndrome, the critical care paradigm: what we learned and what we forgot.** *Curr Opin Crit Care* 2004, **10:**272-278.
118. Gattinoni L, Carlesso E, Cadringher P, Valenza F, Vagginelli F, Chiumello D: **Physical and biological triggers of ventilator-induced lung injury and its prevention.** *Eur Respir J* 2003, **47 (Suppl):**15s-25s.
119. Luecke T, Herrmann P, Kraincuk P, Pelosi P: **Computed tomography scan assessment of lung volume and recruitment during high-frequency oscillatory ventilation.** *Crit Care Med* 2005, **33:**S155-162.
120. Bohm SH, Lachmann B: **Pressure control ventilation: putting a mode into a perspective.** *Int J Int Care* 1996, **4:**45-55.
121. Pelosi P, Goldner M, McKibben A, Adams A, Eccher G, Caironi P, Losappio S, Gattinoni L, Marini JJ: **Recruitment and derecruitment during acute respiratory failure: an experimental study.** *Am J Respir Crit Care Med* 2001, **164:**122-130.
122. Crotti S, Mascheroni D, Caironi P, Pelosi P, Ronzoni G, Mondino M, Marini JJ, Gattinoni L: **Recruitment and derecruitment during acute respiratory failure: a clinical study.** *Am J Respir Crit Care Med* 2001, **164:**131-140.
123. Luecke T, Roth H, Joachim A, Herrmann P, Deventer B, Weisser G, Pelosi P, Quintel M: **Effects of end-inspiratory and end-expiratory pressures on alveolar recruitment and derecruitment in saline-washout-induced lung injury - a computed tomography study.** *Acta Anaesthesiol Scand* 2004, **48:**82-92.
124. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin R, Mascheroni D, *et al.*: **Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure.** *Anesthesiology* 1988, **69:**824-832.
125. Hubmayr RD: **Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story.** *Am J Respir Crit Care Med* 2002, **165:**1647-1653.
126. Durham R, Neunaber K, Vogler G, Shapiro M, Mazuski J: **Right ventricular end-diastolic volume as a measure of preload.** *J Trauma* 1995, **39:**218-223; discussion 223-224.
127. Diebel LN, Wilson RF, Tagett MG, Kline RA: **End-diastolic volume. A better indicator of preload in the critically ill.** *Arch Surg* 1992, **127:**817-821; discussion 821-822.
128. Diebel LN, Myers T, Dulchavsky S: **Effects of increasing airway pressure and PEEP on the assessment of cardiac preload.** *J Trauma* 1997, **42:**585-590; discussion 590-591.
129. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ: **Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation.** *Intensive Care Med* 1992, **18:**142-147.
130. Ferris SE, Konno M: **In vitro validation of a thermodilution right ventricular ejection fraction method.** *J Clin Monit* 1992, **8:**74-80.
131. Goedje O, Hoeke K, Lichtwarck-Aschoff M, Faltchauser A, Lamm P, Reichart B: **Continuous output by femoral arterial thermodilution calibrated pulse contour analysis: comparison with pulmonary arterial thermodilution.** *Crit Care Med* 1999, **27:** 2407-2412.
132. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F: **Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit.** *Am J Respir Crit Care Med* 2002, **166:**1310-1319.
133. Jardin F, Vieillard-Baron A: **Right ventricular function and positive pressure ventilation in clinical practice: from hemodynamic subsets to respirator settings.** *Intensive Care Med* 2003, **29:**1426-1434.
134. Gorcsan J 3rd: **Assessment of left ventricular systolic function using color-coded tissue Doppler echocardiography.** *Echocardiography* 1999, **16:**455-463.
135. Denault AY, Gorcsan J 3rd, Mandarino WA, Kancel MJ, Pinsky MR: **Left ventricular performance assessed by echocardiographic automated border detection and arterial pressure.** *Am J Physiol* 1997, **272:**H138-147.
136. Gorcsan J 3rd, Denault A, Mandarino WA, Pinsky MR: **Left ventricular pressure-volume relations with transesophageal echocardiographic automated border detection: comparison with conductance-catheter technique.** *Am Heart J* 1996, **131:** 544-552.
137. Peters J, Robotham JL: **Hemodynamic effects of increased intrathoracic pressure.** In *Cardiopulmonary Interactions in Acute Respiratory Failure*. Edited by Vincent JL, Suter PM. Berlin-Heidelberg-New York: Springer; 1987:120-133.